PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference GP04-1027PCT		Date of mailing (*day/month/year*) FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/JP2005/000964	International filing date (*day/month/year*) 26.01.2005	Priority date (*day/month/year*) 27.01.2004

International Patent Classification (IPC) or both national classification and IPC

Applicant
ORIENT CANCER THERAPY CO., LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP Facsimile No.	Authorized officer Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 5

because:

☒ the said international application, or the said claims Nos. 5
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claim 5 relates to a method for treatment of the human body by therapy.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 5

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. IV **Lack of unity of invention**

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest
   - ☐ not paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

There are two groups of inventions in the present application.

1. Claims 1-4

A test method for assuming the prognostic effect in immunotherapy for pancreatic cancer characterized by measuring endogenous IL-12 productivity

2. Claims 6-8

A therapeutic agent for cancer comprising gemcitabine hydrochloride as its main ingredient characterized by being used with at least an IL-12 productivity inducing agent

There exists no single general inventive concept between groups 1 and 2 above.

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts
   - ☒ the parts relating to claims Nos. 1-4, 6-8

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4, 6-8	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-4, 6-8	NO
Industrial applicability (IA)	Claims	1-4, 6-8	YES
	Claims		NO

2. Citations and explanations:

Document 1: WO, 2003/030938, A, 17 April, 2003 (17.04.03)
Document 2: JP, 2003-514017, A, 15 April, 2003 (15.04.03), & WO, 2001/035956, A, & EP, 1229908, A

Claims 1-4

Document 1 (particularly, claims 1-18; refer to page 8, lines 32-35, page 12, lines 11-20, page 14, lines 28-37, page 19, lines 36-50) describes that concerning the treatment of pancreatic cancer, IL-12 productivity is emphasized as the meaning of immunotherapy and a marker is established therefor; IL-12 productivity means a function for increasing the IL-12 quantity that a peripheral blood mononuclear cell fraction produces due to its stimulus by 7.8 pg/ml or more; if the IL-12 value is 7.8 pg/ml or more, a cytotoxic T cell (CTL) is active; the cytotoxic T cell (CTL) hinders a cancer cell; and an immunotherapeutic agent for cancer having a β1, 3 glucan structure (β1, 3-1, 6 structure) which is established as a marker by emphasizing the therapeutic meaning of IL-12 productivity.

Document 1 does not describe any prediction of prognostic effect, but the fact that IL productivity is emphasized as its therapeutic meaning means that IL-12 productivity is emphasized for a prognostic effect. So, a person skilled in the art could have easily conceived performing measurement of IL-12 productivity to predict a prognostic effect in an immunotherapy for pancreatic cancer from the description of document 1.

Besides, document 1 does not describe that IL-12 productivity is divided into a plurality of groups, and 50 pg/ml is used as an indicator, but document 1 describes that CTL activation is judged using 7.8 pg/ml as an indicator of IL-12 value. So, a person skilled in the art could have easily conceived of setting another value as required and judging CTL activation.

Claims 6-8

Document 1 (particularly, claim 11; refer to page 19, lines 36-50) describes a constitution in which an immunotherapeutic agent for cancer having the action of inducing IL-12 and an anticancer chemotherapeutic agent which does not hinder the CTL system are used together, and that if the IL-12 value is 7.8 pg/ml or more as IL-12 productivity, a cytotoxic T cell (CTL) is active.

Document 1 does not describe gemcitabine hydrochloride, but gemcitabine hydrochloride itself is publicly known as a chemotherapeutic agent for pancreatic cancer (see the claims of document 2). So, a person skilled in the art could have easily employed gemcitabine hydrochloride as a chemotherapeutic agent described in document 1 for the therapy of pancreatic cancer.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The subject matters of claims 1-4 relate to a test method for assuming the prognostic effect in an immunotherapy for pancreatic cancer characterized by measuring endogenous IL-12 productivity, but the test which is performed in the examples of the specification is not for pancreatic cancer but for bile duct cancer. The relationship between the measurement of endogenous IL-12 productivity and the prediction of a prognostic effect of pancreatic cancer is not adequately supported by the specification.

The subject matters of claims 7 and 8 relate to a therapeutic agent for pancreatic cancer in which an IL-12 productivity inducing agent and gemcitabine hydrochloride are used together, but in the examples of the specification, an IL-12 productivity inducing agent and gemcitabine hydrochloride are used together for a patient with bile duct cancer. The coadministration of an IL-12 productivity inducing agent and gemcitabine hydrochloride for pancreatic cancer is not adequately supported by the specification.

* NOTICES *

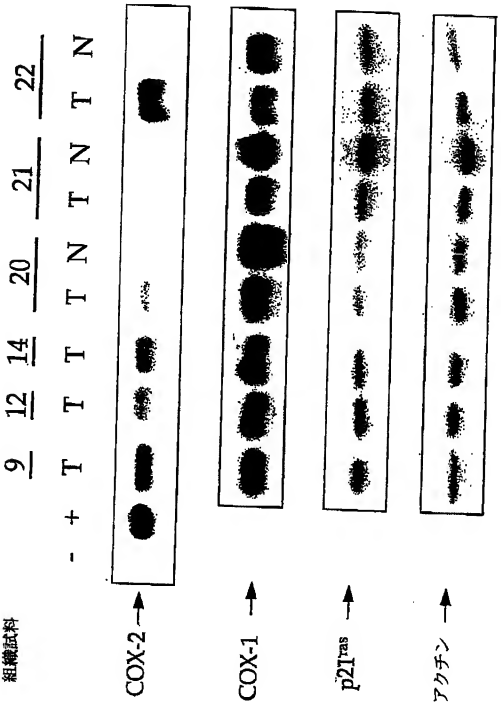
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] How to reduce the viability of a pancreas cancer cell including contacting a cancer cell to NSAID of an effective dose.
[Claim 2] How to raise the susceptibility to the chemotherapic drug of the pancreas cancer cell of the mammals including contacting said cell to NSAID of the effective sensitizing dose.
[Claim 3] The approach according to claim 1 or 2 said NSAID is the sulindac which is COX-2 inhibitor, or its analog.
[Claim 4] The approach according to claim 1 or 2 the cancer cell of said mammals is a Homo sapiens cancer cell.
[Claim 5] The approach according to claim 3 by which a Homo sapiens cancer patient is medicated with said sulindac or its analog.
[Claim 6] The approach according to claim 5 which said cancer patient is treating by the chemotherapic drug.
[Claim 7] The approach according to claim 6 said chemotherapic drug is GEMUSHITABIN.
[Claim 8] The approach according to claim 3 by which said sulindac or its analog is administered orally.
[Claim 9] (a) Step which isolates the 1st part of a pancreas cancer cell from a Homo sapiens pancreas cancer patient;
(b) Step which measures those viability;
(c) Step which medicates said patient with sulindac or its analog;
(d) Step which isolates the 2nd part of a pancreas cancer cell from said patient;
(e) Step which measures the viability of said 2nd part of a pancreas cancer cell;
(f) How to evaluate the capacity of the sulindac which is COX-2 inhibitor in which it is shown including the step in comparison with the viability which measured the viability measured at the step (e) at the step (b) that sensitization of said cell was carried out to said chemotherapic drug by the fall of the viability in a step (e), and which carries out sensitization of the pancreas cancer cell to a chemotherapic drug, or its analog.
[Claim 10] The approach according to claim 9 by which a step (b) and (e) are performed under existence of said chemotherapic drug.
[Claim 11] The approach according to claim 10 said chemotherapic drugs are GEMUSHITABIN and/or 5-FU.

[Translation done.]

Drawing selection drawing 1



[Translation done.]